Association Between Classes of Antidiabetic Medications and Their Potential Risk or Protective Effects on Cancer: A Network Meta-Analysis of Observational Studies

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Introduction

- The mainstay of diabetes treatment is the use of antidiabetic medications, particularly novel antidiabetics that showed promising results in reducing short and long-term diabetes complications.[1]
- Reviews of short-term randomized clinical trials (RCTs) did not indicate an increased risk of cancer with the use of novel antidiabetics.[2]
- The aim of this network meta-analysis (NMA) is to compare the potential cancer risks or protective effects associated with these novel antidiabetic medications, based on observational studies.

Methods

Systematic Review	
Registration / Reporting	• PROSPERO (CRD42023469941). • The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[3]
Databases	• PubMed, Web of Science, and CINAHL until November 15th, 2023.
Inclusion criteria	• Comparative observational (real-world evidence) studies with cancer as outcome. • Have at least one novel antidiabetic in the intervention arm, including sodium-glucose cotransporter-2 inhibitors (**SGLT-2i**), dipeptidyl peptidase-4 inhibitors (**DPP-4i**), and glucagon-like peptide-1 agonists (**GLP-1a**).
Exclusion criteria	• Non-human research, RCTs, case studies, case series, reviews, systematic reviews, and MA.
Network Meta-Analysis (NMA)	
NMA comparators	• Metformin (**Met**), Sulfonylureas (**SUs**), and Thiazolidinediones (**TZDs**).
Bias and Quality assessment	• Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I).[4] • The New Castle–Ottawa Scale (NOS).
Certainty of evidence	• Grading of recommendations, assessment, development, and evaluations (GRADE).[5]
NMA inclusion criteria	• Cohort studies that reported cancer incidence and sample size.
NMA model	• Random-effects model with informative priors (Bayesian framework).
NMA estimate	• Pooled odds ratio (OR) with 95% credible intervals (CrI).
NMA analysis	• WinBUGS 1.4.3. • NetMetaXL 1.6.1.[6]

Results

- 62 observational studies (53 cohort and 9 case-control) were included in the systematic review.
- 22 studies (37 comparisons) with 6,041,368 patients and 24,017 events met the inclusion criteria of our NMA.
- SGLT-2i were likely to reduce the overall cancer risk compared to sulfonylureas (OR:0.54; 95%CrI: 0.40 – 0.74, low certainty), GLP-1a (OR:0.70; 95%CrI: 0.53 – 0.92, low certainty), and DPP-4i (OR:0.72; 95%CrI: 0.57 – 0.92, very low certainty).
- DPP-4i were associated with a lower risk of cancer compared to sulfonylureas (OR:0.76; 95%CrI: 0.60 – 0.96, low certainty).
- SGLT-2i had the highest probability of being the safest (SUCRA= 0.97), followed by metformin (SUCRA= 0.58) and DPP-4i (SUCRA= 0.53). Sulfonylureas had the lowest probability of being the safest, with a SUCRA score of 0.05.
- Most of the studies (93.5%, n=58) were high quality, and (50%, n = 31) had a low or medium risk of bias.

Figure 1 : League table of the overall risk of cancer

97%					
SGLT-2i	**58%**				
0.75 (0.47 – 1.17)	Metformin	**53%**			
0.72 (0.57 – 0.92)	0.96 (0.63 – 1.47)	DPP-4i	**46%**		
0.70 (0.53 – 0.92)	0.93 (0.61 – 1.42)	0.97 (0.76 – 1.24)	GLP-1a	**41%**	
0.67 (0.46 – 1.00)	0.90 (0.54 – 1.52)	0.94 (0.67 – 1.33)	0.97 (0.67 – 1.42)	TZDs	**5%**
0.54 (0.40 – 0.74)	0.72 (0.46 – 1.13)	0.76 (0.60 – 0.96)	0.77 (0.60 – 1.01)	0.80 (0.54 – 1.18)	SUs

SUCRA score
Intervention
Significant OR

Figure 2A : NMA number of patients

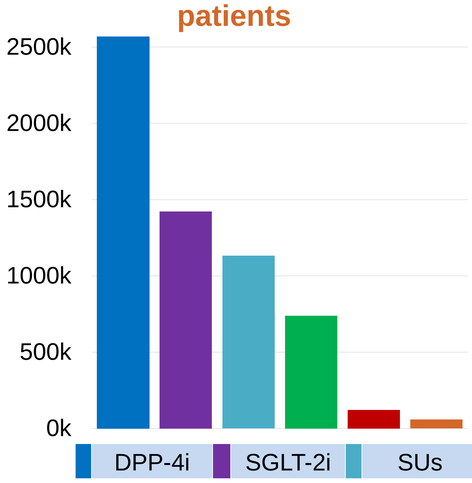


Figure 2B: NMA cancer events

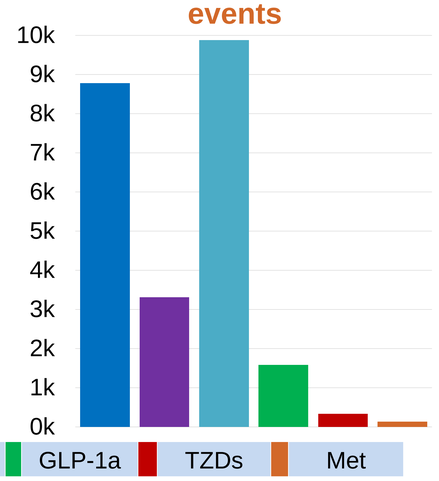
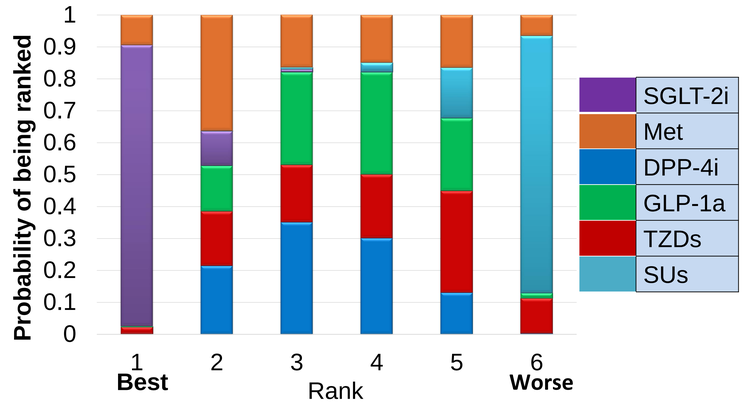


Figure 3: Random effect (Informative) Rankogram



Discussion

- Our results align with the histological evidence that reported the effect of SGLT-2i in eliminating tumor cells.[7]
- Previous reviews of RCTs did not conclude a protective effect of SGLT-2i, probably because they used short-term follow-up data and included other users of SGLT-2i, including patients with heart failure and chronic kidney disease.[2]
- Insufficient control over important confounders and absence of appropriate comparators downgraded the bias and quality assessments for most of the included studies.[4]
- Future research should focus on head-to-head comparisons among these antidiabetics to avoid inconclusive findings.
- These results could influence clinical practice by guiding medication choices with a focus on patient safety.

Conclusion

- SGLT-2 inhibitors are associated with protective effects against developing cancer compared to sulfonylureas, GLP-1a, and DPP-4i.
- Further studies are needed to explore the mechanisms behind this observed association.

References

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